



# Phase behavior and mesoscale solubilization in aqueous solutions of hydrotropes



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## ABSTRACT

Hydrotropes are amphiphilic molecules that are too small to spontaneously form equilibrium structures in aqueous solutions, but form dynamic, non-covalent assemblies, referred to as clusters. In the presence of a hydrophobic compound, these clusters seem to get stabilized leading to the formation of long-lived, highly stable mesoscopic droplets, a phenomenon that we call “mesoscale solubilization”. In this work, we focus on the unusual mesoscopic properties of aqueous solutions of a nonionic hydrotrope, namely tertiary butyl alcohol (TBA), on addition of various hydrophobic compounds. Aqueous TBA solutions, in about 3–8 mol% TBA concentration range and about 0–25 °C temperature range, show the presence of short-ranged (~0.5 nm), short-lived (tens of picoseconds) molecular clusters which result in anomalies of the thermodynamic properties. These clusters are transient but do not relax by diffusion, thus distinctly different from conventional concentration fluctuations. In this concentration and temperature range, upon the addition of a third (more hydrophobic) component to TBA–water solutions, long-lived mesoscopic droplets of about 100 nm size are observed. In this work, we clarify the ambiguity behind the definition of solubility and elucidate the phenomenon of mesoscale solubilization. A systematic study of the macroscopic and mesoscopic phase behavior of three ternary systems TBA–water–propylene oxide, TBA–water–isobutyl alcohol, and TBA–water–cyclohexane has been carried out. We differentiate between molecular solubility, mesoscale solubilization, and macroscopic phase separation. We have confirmed that practically stable aqueous colloids can be created from small molecules, without addition of surfactants or polymers. Such kind of novel materials may find applications in the design of various processes and products, ranging from pharmaceuticals to cosmetics and agrochemicals.

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## 1. Introduction

Hydrotropes are small organic molecules that are known to increase the solubility of hydrophobic compounds in aqueous solutions [1]. Hydrotropes are amphiphilic molecules whose non-polar part is smaller when compared with traditional surfactants [2]. In an aqueous environment, hydrotropes do not spontaneously self-assemble to form stable equilibrium structures, such as micelles [3]. However, above a minimum hydrotrope concentration, they show the presence of a loose, dynamic non-covalent clustering or “micelle-like” fluctuations [4–7]. These micelle-like fluctuations are short-ranged, less than 1 nm in size and short-lived with a lifetime of tens of picoseconds [5,7–9]. Hydrotropes are classified as ionic and non-ionic hydrotropes, with aromatic ionic hydrotropes, such as sodium benzene sulphonate or sodium

benzoate, being traditionally used in the industry [10]. Although there is a wide amount of literature on ionic hydrotropes, the role of the micelle-like fluctuations in aqueous solutions of non-ionic hydrotropes is rarely discussed. Examples of non-ionic hydrotropes include aromatic alcohols such as resorcinol, and amides such as urea [11,12]. In this work, we extend the definition of non-ionic hydrotropes to include short-chain alcohols such as *n*-propanol, *iso*-propanol, tertiary butyl alcohol, 2-butoxyethanol, amines such as 3-methylpyridine, and ethers such as tetrahydrofuran.

This work focuses on the properties of a specific non-ionic hydrotrope, namely tertiary butyl alcohol (TBA). TBA is the highest molecular weight alcohol to be completely miscible with water in all proportions under ambient conditions [13]. Recently, molecular dynamics simulations have shown the presence of micelle-like fluctuations over a dilute concentration range, 3–8 mol% (11–26 mass%) TBA in water [7]. Numerous experimental studies and other simulations support this picture [14–20]. Micelle-like structural fluctuations lead to anomalies in the thermodynamic properties of TBA–water solutions [7]. Thermodynamic properties such as activity coefficients, chemical potentials, and heat

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capacity, show extrema in this concentration range and at temperatures below room temperature [21–27].

Furthermore, under certain conditions aqueous TBA solutions show the presence of mesoscopic droplets, with a size of about 100 nm [28–35]. We have recently shown that mesoscopic droplets form only when a hydrophobic compound (“hydrophobe”) is added to aqueous TBA solutions in the concentration range of 3–8 mol% TBA and at low temperatures (below room temperature), thus clarifying the long-standing issue on the origin of mesoscopic inhomogeneities in such solutions [34,35]. The hydrophobe seems to stabilize the micelle-like fluctuations leading to formation of the mesoscopic droplets. We call the phenomenon of formation of mesoscopic droplets in aqueous solutions of hydrotropes with addition of a hydrophobe, as mesoscale solubilization.

Mesoscale solubilization is not unique to aqueous TBA solutions, but has been observed across various hydrotrope–water solutions that contain hydrophobic compounds. Yang et al. have observed the presence of mesoscopic droplets, 100 s of nm in size, in aqueous solutions of tetrahydrofuran and 1,4-dioxane [36]. Sedláč has carried out extensive static and dynamic light scattering experiments in around 100 different solute–solvent pairs and observed the presence of mesoscopic droplets in aqueous solutions of various electrolytic and non-electrolytic solutions [37–39]. Jin et al. carried out a static and dynamic light scattering study in aqueous solutions of tetrahydrofuran, ethanol, urea, and  $\alpha$ -cyclodextrin and observed mesoscopic droplets in these solutions, which they interpreted as gaseous nanobubbles [40]. In our previous work, we have clarified that such observed mesoscopic droplets in aqueous solutions of non-ionic hydrotropes are caused by the contamination of the non-ionic hydrotrope by trace amounts of hydrophobic impurities [34,35].

In this paper, we elucidate the phenomenon of mesoscale solubilization. We aim to clarify the ambiguity of the conventional definition of solubility by differentiating between molecular solubility and molecular clustering on the one hand, and macrophase separation and mesoscale solubilization on the other hand. We define mesoscale solubilization as the formation of mesoscopic droplets (order of a hundred nm in size) that leads to increased effective solubility of hydrophobic compounds in aqueous solutions of non-ionic hydrotropes. The thermodynamic stability of mesoscopic droplets in aqueous solutions of TBA in the presence of several hydrophobic compounds is discussed. Ternary phase behavior of three different systems have been studied: (1) TBA–water–propylene oxide; (2) TBA–water–isobutyl alcohol; (3) TBA–water–cyclohexane. In addition to determining the macroscopic ternary phase diagrams, the macroscopically homogeneous one-phase regions have also been characterized, via static and dynamic light scattering, to clarify the nature of the mesoscale solubilization.

## 2. Experimental

### 2.1. Materials

TBA with a labeled purity of 0.998+ was purchased from Alfa Aesar. Propylene oxide (PO) with a labeled purity of 0.995+ was purchased from Sigma–Aldrich. Isobutyl alcohol (IBA) with a labeled purity of 0.999+ was purchased from J.T. Baker. Cyclohexane (CHX) with a labeled purity of 0.990+ was purchased from Merck. Deionized water was obtained from a Millipore setup.

For light scattering experiments, the binary TBA–water solutions were filtered with 200 nm Nylon filters to remove dust particles. An additional filtration with 20 nm Anopore filters was carried out only if the TBA–water solutions showed mesoscopic droplets due to the presence of hydrophobic impurities in TBA (as

was shown in Ref. [35]). The third component, PO, IBA, or CHX was added to the filtered TBA–water solution. PO was used without filtration because of its high volatility (boiling point 34 °C [41]), while IBA and CHX were used after filtering them with 200 nm Nylon filters. Light scattering measurements were performed after equilibrating the samples for about 24 h.

The refractive index was measured with an Abbe refractometer at room temperature. The viscosity of the samples was measured with a Ubbelohde viscometer in a temperature controlled ( $\pm 0.2$  °C) water bath.

### 2.2. Determination of phase diagram

The ternary phase diagram for each of the three systems was determined by the cloud-point method [42]. The third component was added to a binary mixture in small steps. At each step, the ternary mixture was manually shaken and let to rest for about 3–5 min. The sample was then visually observed to determine if phase transition had occurred. If not, more of the third component was added and the above procedure was repeated. The ternary phase diagram of TBA–water–PO system was determined at 25 °C, with an accuracy of  $\pm 0.1$  °C. The phase diagrams of TBA–water–IBA and TBA–water–CHX were determined at 21 °C, with an accuracy of  $\pm 0.5$  °C. In order to estimate the location of the critical point, light scattering experiments were carried out in the macroscopic one-phase region close to the binodal curve. If the correlation length of critical fluctuations exhibited a maximum, then the point of the binodal curve corresponding to this maximum was interpreted as the critical point.

### 2.3. Light scattering

Static and dynamic light scattering experiments were performed with a PhotoCor Instruments setup, as described in Ref. [34]. Temperature was controlled with an accuracy of  $\pm 0.1$  °C. The Photocor correlator computes an intensity auto-correlation function  $g_2(t)$ , which is an instrumental output that can be further analyzed (as shown below) to determine the size of aggregates undergoing Brownian motion in a system at thermodynamic equilibrium. For two exponentially decaying relaxation processes, auto-correlation function  $g_2(t)$ , obtained in the self-beating (homodyne) mode, can be written as [43,44]:

$$g_2(t) - 1 = \left[ A_1 \exp\left(-\frac{t}{\tau_1}\right) + A_2 \exp\left(-\frac{t}{\tau_2}\right) \right]^2 \quad (1)$$

where  $A_1$  and  $A_2$  are the amplitudes of the two relaxation processes,  $t$  is the “lag” (or “delay”) time of the photon correlations and  $\tau_1$  and  $\tau_2$  are the characteristic relaxation times. For a diffusive process, the relaxation time  $\tau$  is related to the diffusion coefficient,  $D$ , as follows [43,44]:

$$\tau = \frac{1}{Dq^2} \quad (2)$$

where  $q$  is the difference in the wave number between incident and scattered light,  $q = (4\pi n/\lambda) \sin(\theta/2)$ ,  $n$  is the refractive index of the solvent,  $\lambda$  is the wavelength of the incident light in vacuum ( $\lambda = 633$  nm for our set-up) and  $\theta$  is the scattering angle. For monodisperse, non-interacting, spherical Brownian particles the hydrodynamic radius  $R$  can be calculated with the Stokes–Einstein relation [43,44]:

$$R = \frac{k_B T}{6\pi\eta D} \quad (3)$$

where  $k_B$  is Boltzmann’s constant,  $T$  is the temperature and  $\eta$  is the shear viscosity of the medium.

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